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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,043	CANTOR ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/30/07; 4/10/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-24 are pending and examined on the merits.

This Office Action is in reply to Applicants' correspondence of 4/07/2008.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put the application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is made **FINAL**.

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification – Withdrawn Objection

1. The objection to the disclosure as containing an embedded hyperlink and/or other form of browser-executable code, as set forth in the previous Office Action, is **WITHDRAWN** in light of the amendments to the specification.

Withdrawn Claim Objections

2. The objection to claim 17, as set forth in the previous Office Action, is **WITHDRAWN** in light of the amendments to claim 17.

Withdrawn Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

3. The rejections of claims 1-11, 17 and 18 under 35 U.S.C. 112, second paragraph, as set forth in the previous Office Action, are **WITHDRAWN** in light of the amendments to the claims.

New Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

4. Claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8 and 19-24 are unclear over the recitation of the phrase 'genotyping the polymorphic site in the at least the first nucleic acid region and the second nucleic acid region thereby resulting in at least a first, a second, and a third genotype', because it is unclear how genotyping a first and second region results in a first, second, and third genotype. The claim may be made more clear if the unclear phrase is amended to recite 'genotyping the polymorphic site in the at least the first nucleic acid region the second nucleic acid region and the third nucleic acid region thereby resulting in at least a first, a second, and a third genotype'.

Claims 4-6 are unclear over recitation of the phrase 'the polymorphic marker is a' as recited in each of claims 4-6. Claim 1, from which rejected claims 4-6 depend requires 'at least three polymorphic markers', thus it is unclear which of the specifically required polymorphic markers is 'the polymorphic marker'. The claims may be made more clear if the unclear phrase is amended to recite 'the polymorphic markers are' followed by recitation of the plural form of the different types of polymorphic markers (e.g.: the polymorphic markers are single nucleotide polymorphisms).

Claim 24 is unclear over recitation of the phrase 'the region flanked by the first, the second, and the third nucleic acid is about 100 bp long'. Claim 1, from which the rejected claim depends, requires three primer pairs each of which flanks a nucleic acid

region, and amplification of a nucleic acid molecule with the primer pairs. However the unclear phrase requires that a region is flanked by 'the first, the second, and the third nucleic acid'. The claim may be made more clear is amended to recite 'the region flanked by the first, the second, and the third primer pairs is about 100 bp long'.

Withdrawn Claim Rejections - 35 USC § 102

5. The rejection of claims 1, 2, and 4-6 under 35 U.S.C. 102(b), as being anticipated by Ruano et al (1990) as set forth in the previous Office Action is **WITHDRAWN** in light of the amendments to the claims to require at least three primer pairs to amplify different nucleic acid regions.

New Claim Rejections - 35 USC § 103

6. Claims 1, 2, 4-6, 8, and 21, 22, 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruano et al (1990) in view of Furlong et al (1993).

Ruano et al teaches a method for the analysis of haplotypes amplified from a single DNA molecule.

Regarding claim 1, Ruano et al teaches that a nucleic acid sample from a subject is diluted to form a solution containing a single copy of the target molecule (p.6297 – Dilutions; Fig 3), relevant to step (a). Relevant to step (b), the reference teaches the amplification of target DNA using two primer pairs (GR1, GR3 and GR2, GR4) that amplify a region comprising 3 polymorphic sites (i.e.: primers GR1 and GR3 type a TG deletion; primers GR2 and GR4 type two separate SNPs) (Fig 1; p.6297 – Target for

amplification). Further relevant to step (b), the reference teaches that distant segments of an intact template molecule can be analyzed by PCR with multiple primer pairs for direct haplotype determination (p.6300 – Discussion). Relevant to step (c), Ruano et al teaches the genotyping of sites amplified from the single molecule dilution target DNA by southern hybridization (Fig 4) and restriction digestion (Fig 3). Relevant to step (d), the reference teaches that information regarding the individual genotypes is combined to determine the haplotype of the subject (Fig 4; p.6298 – Typing and direct haplotype determination of SMP products).

Regarding claim 2, Ruano et al teaches that additional experiments are performed on sample DNA to resolve constituent haplotypes of heterozygous individuals (p.6298, right col., last paragraph; Fig. 3; Fig 4), and that each experiment followed the scheme present in Figure 3 of the reference, thus comprising steps (a)-(c) as recited in claim 1. The reference specifically teaches that for 'Person B' the experiment was repeated five times, and that four haplotypes (each comprising the component genotypes) were resolved (Fig 4; p.6299 – Individual B). The comparison of multiple deduced haplotypes to determine the haplotype of the subject is a statistical analysis.

Regarding claims 4-6, Ruano et al teaches the analysis of a haplotype comprising polymorphic sites that are single nucleotide polymorphisms and a dinucleotide insertion/deletion (Fig 1).

Ruano et al does not specifically teach the analysis of at least three polymorphic markers that are about one or more kilo base pairs apart (as recited in the preamble of

claim 1), or the amplification of a single molecule dilution with at least three primer pairs that each amplify a different nucleic acid region that comprises at least one polymorphic site (step (b) of claim 1). Ruano et al does not exemplify producing 12-18 replica genotypes (claim 8), polymorphic markers that are three or more, or four or more kilo base pairs apart (claims 21 and 22), or flanked regions that are about 100 bp long (claim 24). However such methods where well known in the art at the time the invention was made.

Furlong et al teaches the haplotype analysis of flow sorted single sperm cells (p.1192 – Flow sorting single sperm), which contain a single molecule dilution of each human chromosome. Relevant to the required limitations of the rejected claims, Furlong et al teaches amplifying nucleic acid from a single sperm cell with at least three primer pairs (p.1192 – PCR primers) that each amplify a different nucleic acid region that comprises at least one polymorphic site (step (b) of claim 1); and teaches the amplification of the polymorphic loci D9S109, D9S127, and D9S53, which are polymorphic loci that are about one or more kilo base pairs apart (claim 1) and three or more kilo base pairs apart (claim 21) and four or more kilo base pairs apart (claim 22). Relevant to the requirements of step (b) of claim 1, Furlong et al teaches the amplification of a single sperm cell nucleic acids with at least three primer pairs that each amplify a different nucleic acid region that comprises at least one polymorphic site (p.1192 – PCR of single sperm). Regarding claim 24, though required claim limitations have been addressed earlier in this Office Action in light of 35 USC 112 2nd ¶, it is

noted that Furlong et al teaches amplification using primers that flank a nucleic acid region of about 100 base pairs.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have performed the haplotype of the analysis of the polymorphic markers as taught by Furlong et al, including amplification using at least three primer pairs, incorporating the single molecule dilution and genotype analysis of Ruano et al. One would have been motivated to analyze the markers as taught by Furlong et al based on the teachings of Furlong et al that the markers may be associated with epithelioma (p.1191, right col.). One would have been motivated to use the multiple pairs of primer based on the teachings of Ruano et al that distant segments in an molecule are amenable to PCR with multiple primer pairs for direct haplotyping (p.6300, left col., Discussion).

Regarding claim 8, Ruano et al teaches repetition of experimentation to resolve genotypes (p.6298 – right col., last paragraph), and further teaches that errors in haplotype determination should be held in check by analyzing replicate vials (p.6300, left col., lns.43-45). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the haplotype determination methods of Ruano et al to produce and analyze 12-18 replicas. One would have been motivated to create multiple genotype replicas based on the assertion of Ruano et al that such methods increase the accuracy of the analysis (p.6298 – right col., last paragraph; p.6300, left col., lns.43-45). One of skill in the art would recognize that creating an increased number of replica genotypes would lead to further increased

accuracy of haplotype determination, and the skilled artisan would be capable of creating, for example, 12 genotype analyses of single-molecule dilutions (e.g. Ruano et al teaches twelve total analyses in Fig 4).

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 102 as anticipated by the teachings of Ruano et al. Applicants arguments (p.10-11 of the Remarks) are largely moot as the previous rejection has been with drawn in light of the amendments to the claims, and the claims are now rejected as obvious in light of Ruano et al in view of Furlong et al. However, it is relevant to address some of Applicants arguments in light of the newly set forth rejection. Furlong et al teaches methods related to the methods of Ruano et al (i.e. direct haplotype determination using single DNA templates and PCR amplification). Furlong et al provides for the analysis of nucleic acids for haplotype determination comprising multiple primer pairs, a method alluded to by Ruano et al (as addressed in the rejection). Applicants have asserted that the methods of Ruano et al require a booster PCR and are applicable only to short amplicons, and that amplification of single nucleic acid molecules is not reliable (Remarks p. 11). It is noted that Furlong et al, as cited in the instant rejection, demonstrates amplification of single nucleic acid molecules in a multiplex reaction. And while Applicants argue (p.11 of Remarks) the efficiency of amplification of 'very short fragments', it is noted that there is no such limitation in any of the claims. Given the explicit teachings and examples of Furlong et al, Applicants' argument concerning the

alleged problems with amplification of single nucleic acid molecule dilutions using two or more primer pairs are not applicable to the rejection as set forth.

7. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ruano et al (1990) (citation no. 30 on the IDS of 07/31/2006) in view of Furlong et al (1993) as applied to claims 1, 2, 4-6, 8, 21, 22, and 24 above, and further in view of Ross et al (citation no. 27 on the IDS of 07/31/2006).

The teachings of Ruano et al in view of Furlong et al are applied to claim 7 as they were previously applied to claims 1, 2, 4-6, 8, 21, 22, and 24.

Ruano et al in view of Furlong et al does not teach the analysis of amplified polymorphic genotype markers using primer extension and mass spectrometric detection.

Ross et al teaches methods of multiplex genotyping using primer extension and mass spectrometry (p.1347, right col., lns.3-11). The reference teaches a method comprising the steps of amplification of 12 polymorphic loci and subsequent primer extension using oligonucleotide primers and ddNTPS (p.1350 – Experimental protocol, PCR). The reference further teaches analysis of the primer extension products by MALDI-TOF mass spectrometry (p.1350 – Experimental protocol, MS; Fig.2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the haplotype analysis methods of Ruano et al in view of Furlong et al so as to have incorporated the primer extension/mass spectrometry based genotype detection methods of Ross et al. One would have been

motivated to use the methods of Ross et al based on the teachings of Ross et al that primer extension/mass spectrometry based methods eliminate excess handling and can resolve many possible genotypes/loci using a single non-fluorescent primer (p.1347, left col., ln.37).

Response to Remarks

Applicants' traversal (p.12 of Remarks) of the rejection of claims under 35 USC 103 as obvious in light of Ruano et al in view of Ross et al is moot in light of the newly set forth rejection.

8. Claims 3, 9-11, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruano et al (1990) (citation no. 30 on the IDS of 07/31/2006) in view of Furlong et al (1993) as applied to claims 1, 2, 4-6, 8, 21, 22, and 24 above, and further in view of Drysdale et al (2000) (citation no. 9 on the IDS of 07/31/2006).

The teachings of Ruano et al in view of Furlong et al are applied to claims 3, 9-11, 19 and 20 as they were previously applied to claims 1, 2, 4-6, 8, 21, 22, and 24.

Ruano et al teaches a method for the determination of haplotypes amplified from a single DNA molecule and methods to obtain at least four genotype replicas, thus teaching all of the limitations of claims 1 and 2 (from which rejected claim 3 depends), as well as steps (a)-(d) of claim 9, and the limitations of claim 10, where the analysis of multiple deduced haplotypes to determine the haplotype of the subject is a statistical analysis.

Regarding the limitations of claim 11, Ruano et al teaches repetition of experimentation to resolve genotypes (p.6298 – right col., last paragraph), and further teaches that errors in haplotype determination should be held in check by analyzing replicate vials (p.6300, left col., lns.43-45).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the haplotype determination methods of Ruano et al to produce and analyze 12-18 replicas. One would have been motivated to create multiple genotype replicas based on the assertion of Ruano et al that such methods increase the accuracy of the analysis (p.6298 – right col., last paragraph; p.6300, left col., lns.43-45). One of skill in the art would recognize that creating an increased number of replica genotypes would lead to further increased accuracy of haplotype determination, and the skilled artisan would be capable of creating, for example, 12 genotype analyses of single-molecule dilutions (e.g. Ruano et al teaches twelve such analyses in Fig 4).

Ruano et al in view of Furlong et al does not teach the comparison of a deduced haplotype with a haplotype from a control or a database of haplotypes from controls to determine association of the haplotype with a biological trait (as required by claim 3), or comparison of a deduced haplotype with known disease-associated haplotypes to indicate that the subject has, or is susceptible for, a disease (as required by step (e) of claim 9). Ruano et al in view of Furlong et al does not teach an anlysis comprising at least 5 or at least 10 primer pairs (claims 19 and 20).

Drysdale et al teaches the use of β_2-adrenergic (β_2AR) receptor haplotypes comprised of 13 polymorphic positions in the prediction of response to albuterol (p.10486, left col., lns.6-8), which is a biological trait.

Regarding claim 3 and step (e) of claim 9, Drysdale et al teaches a collection of (β_2AR) haplotype pairs found in a cohort of asthmatics (p.10486, right col., lns.3-10; Table 2) (thus a database of haplotypes), as well as the association of the five most common haplotype pairs with patient response to albuterol (Fig.3; p.10487, left col., lns.1-25). The reference further teaches comparing a haplotype to the database of haplotypes and association data to determine association of the haplotype with a biological trait (Fig.3; p.10487, left col., lns.25-30).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have compared haplotypes determined by the methods of Ruano et al to a database of haplotypes as taught by Drysdale et al. One would have been motivated to perform a comparison of a haplotype determined by the methods of Ruano et al with a haplotype from a control, or with known disease-associated haplotypes, based on the assertion of Drysdale et al that haplotypes are more predictive of phenotype, and that individual SNPs may have poor predictive power as pharmacogenetic loci (p.10488, right col., lns.13-17). With specific regard to claim 11, it would have been obvious to create and analyze numerous replicas in a comparison of a haplotype determined for a subject with known disease-associated haplotypes, including producing 12-18 replicas, to increase the accuracy of the analysis, as discussed earlier in this rejection. With specific regard to the requirements of claims 19

and 20, applying the teachings of Furlong et al (i.e. multiplex PCR using primer pairs for each polymorphic marker) to the analysis of Drysdale et al (i.e. analysis of haplotypes comprised of 13 polymorphic markers) would result in a method in which primer pairs flanking each polymorphic site are used to genotype the sample, which is a method in which at least 5 (claim 19) and at least 10 (claim 20) primer pairs are used each to amplify a different nucleic acid region.

9. Claims 12-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruano et al (1990) (citation no. 30 on the IDS of 07/31/2006) in view of Furlong et al (1993) as applied to claims 1, 2, 4-6, 8, 21, 22, and 24 above, and further in view of Rein et al (1998) (citation no.26 on the IDS of 07/31/2006) and Buckholz et al (1997).

The teachings of Ruano et al in view of Furlong et al are applied to claims 12-18 as they were previously applied to claims 1, 2, 4-6, 8, 21, 22, and 24.

Ruano et al teaches a method for the determination of haplotypes amplified from a single DNA molecule and methods to obtain at least four genotype replicas, thus teaching the limitations of steps (b)-(e) of claim 12 and claim 13. Ruano et al teaches the limitations of steps (b)-(e) of claim 17 (with regard to step (c) of claim 17, the teachings of Ruano et al with amplification of the diluted nucleic acid sample is discussed above, and the reference also teaches amplification of an undiluted nucleic acid sample (e.g. Fig 2) as required by step (c) of claim 17) and methods to obtain at least four genotype replicas, as required by claim 18, where the analysis of multiple deduced haplotypes to determine the haplotype of the subject is a statistical analysis..

Regarding the limitations of claim 14 (requiring that 12-18 genotype replicas are produced), Ruano et al teaches repetition of experimentation to resolve genotypes (p.6298 – right col., last paragraph), and further teaches that errors in haplotype determination should be held in check by analyzing replicate vials (p.6300, left col., lns.43-45); although Ruano et al does not specifically teach producing 12-18 replica genotypes by repetition of the diluting, amplifying, genotyping steps.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the haplotype determination methods of Ruano et al to produce and analyze 12-18 replicas, as required by claim 14. One would have been motivated to create multiple genotype replicas based on the assertion of Ruano et al that such methods increase the accuracy of the analysis (p.6298 – right col., last paragraph; p.6300, left col., lns.43-45). One of skill in the art would recognize that creating an increased number of replica genotypes would lead to further increased accuracy of haplotype determination, and the skilled artisan would be capable of creating, for example, 12 genotype analyses of single-molecule dilutions (e.g. Ruano et al teaches twelve such analyses in Fig 4).

Ruano et al in view of Furlong et al does not teach methods of comprising treating a sample with a composition that differentially affects an epigenetically modified nucleotide (step (a) of claim 12), or using bisulfite (claim 16) to modify a methylated nucleotide (claim 15), or digesting a nucleic acid sample with a methylation-sensitive restriction enzyme (step (a) of claim 17).

Rein et al teaches method for the identification of 5-metyhlcytosine and related modifications in DNA genomes (Table 1; p.2255, right col., first full paragraph).

Regarding claim 12, Rein et al teaches methods for analysis of 5-methylcytosine (m^5C, which is a modified nucleotide) by treating genomic DNA with a composition that differentially affects epigentically modified nucleotides by converting non-methylated C to U, and not altering m^5C (p.2258 – Differential base modification by bisulfite), relevant to step (a) of claim 12. Rein et al thus teaches effectively creating polymorphisms (the content at a given nucleotide position can be a C if the position is methylated, or U (which behaves similar to a T in subsequent base pairing processes) if the position is nonmethylated) based on the epigenetic methylation modification (Fig 2).

Regarding claim 15, Rein et al teaches the analysis of 5-methylcytosine (m^5C), which is a methylated nucleotide (p.2258 – Differential base modification by bisulfite).

Regarding claim 16, Rein et al teaches the use of bisulfite for the treatment of a nucleic acid sample (p.2258 – Differential base modification by bisulfite; Table 1; p.2255, right col., ln.25).

Regarding claim 17, Rein et al teaches methods for analysis of methylated bases at specific DNA sites use modification-sensitive restriction endonucleases (Table 1; p.2257 - Modification-sensitive restriction endonucleases (MSREs); Fig 1). Relevant to step (a) of claim 17, the reference teaches the digestion of a sample with restriction enzymes that are sensitive to base modification (i.e. will not digest methylated sites) and restriction enzymes that require base modification (i.e. will only digest methylated sites) (p.2257, left col., lns.14-24; Fig 1). Relevant to step (e) of claim 17, Rein et al

teaches the analysis of the methylation dependent digestion of a sample by Southern analysis and PCR amplification (Fig 1; p.2258, left col., lns.15).

Furthermore, the relevance of specific epigenetically modified methylation sites was known in the prior art at the time the invention was made. Bucholz et al teaches the analysis of several epigenetically modified methylation sites (e.g. p.118 - Table I) greater that are about one or more kilo base pairs apart in the analysis of genomic imprinting and Prader Willi syndrome.

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the haplotype determination methods of Ruano et al and Furlong et al so as to have included the methylation analysis methods of Rein et al and Buckholz et al. One would have been motivated to do so because Rein et al teaches that the status of methylation of any particular cytosine (i.e. 5-methylcytosine) in the genomes of eukaryotic cells plays a role in a variety of processes (p.2255, left col., first paragraph of introduction), where Buckholz et al provides specific loci and positions of relevant methylations. One would have been motivated to use the bisulfite treatment of Rein et al (relevant to claims 12-16) because Rein et al teaches that such methods are highly sensitive, are amenable to rapid genomic sequencing, and provide positive display of m^5C (Table 1). One would have been motivated to use the MSRE method of Rein et al (relevant to claim 17 and 18) because Rein et al teaches that such methods provide a rapid analysis of large DNA regions, and are highly sensitive. With particular regard to step (e) of claim 17, the combination of the restriction enzyme digestion methods of Rein et al (as summarized in Fig 1 of Rein et al) and the haplotype

determination methods of Ruano et al would create a method where, for example, the DNA sample amplified by GR1, GR2, GR3, and GR4 (as from the nomenclature of Ruano et al) would be produce by restriction digestion (as taught in Fig 1 of Rein et al) instead of by a first PCR amplification with GR5 and GR6 (as taught by Fig 1 of Ruano et al). Thus the determined haplotype would include polymorphic markers such as SNPs (determined by PCR as taught by Ruano et al) that are next to (e.g. the polymorphic sites would be adjacent to the cut site determined by the action of an m^5C-requiring restriction enzyme) the methylation site analyzed by the restriction enzyme.

10. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ruano et al (1990) (citation no. 30 on the IDS of 07/31/2006) in view of Furlong et al (1993) as applied to claims 1, 2, 4-6, 8, 21, 22, and 24 above, and further in view of Gerhard et al (1984).

The teachings of Ruano et al in view of Furlong et al are applied to claim 23 as they were previously applied to claims 1, 2, 4-6, 8, 21, 22, and 24.

Ruano et al in view of Furlong et al does not specifically provide for one polymorphic site in a first nucleic acid region that is 15-20 kilo base pairs apart from a polymorphic site in a second nucleic acid region.

However, at the time the invention was made haplotype comprising polymorphic positions that are 15-20 kilo base pairs apart were well known in the art. Gerhard et al teaches a B-globin haplotype including polymorphic positions that are 15-20 kilo base pairs apart (Fig 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Ruano et al in view of Furlong et al to analyze the haplotype comprising of markers in the B-globin cluster as taught by Gerhard et al. One would have been motivated to analyze the markers of Gerhard et al based on the teachings of Gerhard et al that such analyses may provide insight into the distribution if and mechanics underlying meiotic crossing over.

Withdrawn Double Patenting

11. The provisional rejection of claims under Double Patenting over the claims of conflicting application 10/759,519, as set forth in the previous Office Action is **WITHDRAWN** in light of the amendments to the claims of the instant application.

New Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-18, 21, 22, and 24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-6, 9, 12, 15-17, and 20 of U.S. Patent Application No. 10/759,519 in view of Furlong et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the conflicting application recite methods for determining a haplotype of a subject by diluting a sample into a single molecule dilution, amplifying polymorphic sites in the diluted nucleic acid, determining the genotype of the polymorphic sites in the single molecule dilution, determining and a haplotype from the genotypes. The claims of the conflicting application further encompass obtaining replica genotypes, using primer extension and mass spectrometry, comparing determined haplotypes to haplotypes of control subjects and to databases of disease associated haplotypes, as well as the analysis of nucleic acids using bisulfite to modify methylated cytosine and methylation specific restriction enzymes.

The claims of the conflicting application do not require that the genotype polymorphic markers are about one or more kilo base pairs apart, as required by the claims of the instant application. However, the analysis of haplotypes of markers that are separated by the distances required by the rejected claims was well known in the art at the time the invention was made and is taught by Furlong et al.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of the claims of the conflicting

application to analyze the polymorphic markers as taught by Furlong et al. One would be motivated to analyze the markers of Furlong et al based on the assertion of Furlong et al that the markers are in a locus associated with epithelioma.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

13. No claim is allowable. No claim is free of the prior art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days.

Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and

history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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